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TITLE: Detection of Early lung Cancer Among Military Personnel (DECAMP)

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14. ABSTRACT - The purpose of this work is to develop and validate molecular biomarkers found in blood, other bodily fluids, or tissues, which may be used for the early detection of lung cancer in Military Treatment Facilities and Veteran's Administration Hospitals. Over the course of the first year of this award, we have developed the infrastructure needed for launching two distinct clinical trials via establishment of detailed protocols, CRFs and SOPs for both studies. Project 1 will recruit 500 patients with indeterminate pulmonary nodules, identifying 75 with lung cancer and 75 matched controls, to validate existing diagnostic biomarkers in the blood and airway. The ACRIN- and HRPO-approved protocol for Project 1 has been submitted to local IRBs at each site, with several sites having received approval and set to begin recruitment post-training. Protocol 2 will recruit a cross-sectional cohort of smokers with early stage lung cancer (n=50) and matched controls (n=30) along with a longitudinal cohort of 850 high-risk smokers in order to develop molecular biomarkers for the preclinical detection of lung cancer. This protocol has been approved by HRPO and ACRIN and has been submitted to local IRBs. We have further developed the administrative infrastructure to support clinical and imaging data collection at each site along with biosample collection and shipping between the clinical and research sites. This work has set the stage for developing less-invasive measures for the early detection of lung cancer, ultimately decreasing the number of deaths attributable to the disease.

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Introduction:

The purpose of this work is to develop and validate molecular biomarkers that may be used for the early detection of lung cancer. By recruiting approximately 500 patients with indeterminate pulmonary nodules from Military Treatment Facilities and Veteran's Administration Hospitals, DECAMP plans to identify 75 patients with lung cancer for our molecular studies. For the study to develop tests that can identify the patients at highest risk for having or developing lung cancer, DECAMP will recruit approximately 850 high-risk current and former smokers from these same hospitals, determine whether they have lung cancer now and then follow them annually for up to four years to determine if they develop lung cancer. We expect to identify 50 patients who did not have cancer when they join the study, but develop lung cancer while they are being monitored. The clinical applications of this study will come from the development of tests to more accurately diagnose disease at an early potentially curable stage but also predict the occurrence of lung cancer in the future. Additionally, these biomarkers found in blood, other body fluids, or tissues will be collected more easily and are less invasive than surgery. Non-invasive collection of biological samples will be less painful for the patient and allow easier and more frequent monitoring of disease. The intent of this research is to develop early detection strategies that will ultimately decrease lung cancer deaths. This will improve the health and welfare of the military, and the American public as a whole.

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Body:

Over the course of the first year of this award, we have developed the infrastructure needed for launching both clinical trials. We have created detailed protocols and SOPs for both studies and have modified the proposed study design of both studies to respond to the emerging needs of our clinical sites as well as guidance from our external advisory board (EAB). Specifically, we have modified protocol 1 to limit the inclusion criteria to pulmonary nodules that are between .7-2cm in size (from the prior range of .5-2cm), in order to enrich for potential cancer cases. In protocol 2, we have added a second cross-sectional cohort of subjects with early stage lung cancer undergoing surgical resection of their tumors (matched to smokers undergoing resection of benign lung lesions) in order to accelerate discovery efforts for preclinical lung cancer detection biomarkers. We have also reduced the size of our longitudinal cohort to 850 high-risk smokers in order to provide more resources to the MTFs for patient recruitment. We have also added optional biospecimen collection protocols for PBMC and urine (for metabolomics) collection based on feedback from the broader lung cancer biomarker community and the EAB.

The first study protocol has received regulatory approval from both the DoD and ACRIN and has been submitted to all local IRBs. A number of sites have received regulatory approval for this protocol and we anticipate all sites having approval by November 30, 2012. Protocol 2 has been approved by the DoD and ACR, and has recently been submitted to all local IRBs. In order to operationalize both clinical trials, ACRIN has developed a biospecimen collection kit that is being distributed to all clinical sites along with a biospecimen tracking system. They have also developed a detailed questionnaire and CRFs to collect relevant clinical data based on feedback from the EAB. Research Associates have been hired to support the clinical trials at all four of the MTFs. We have completed the training of all clinical sties via webinar and have begun site visits to help launch patient recruitment efforts for protocol 1. A summary of our progress related to each of the tasks in our SOW is included below.

Task 1 Pre-Award Study Development
1a Attended planning meeting hosted by the USAMRMC to present the clinical projects proposed to the four military hospitals and develop the operational features of the Consortium (June 2011)
1b Developed final draft clinical trial protocols for the two proposed studies
1c Developed Case Report Forms (CRFs)
1d Finalized modified budgets in order to provide the necessary resources to the military hospitals

Task 2 Protocol Development (Month 0-6)
2a Received approval for submitted protocols for both clinical projects to Army Surgeon General's Human Research Protection Office (HRPO);
2b Received approval for submitted protocols for both clinical projects to ACR IRB;
2c Submitted Protocol 1 to BU IRB; responded to requests for additional information; currently awaiting pending approval.

Task 3 Clinical Trial Development (Month 0-6)
3a Coordinating Center Activities
- Established Steering Committee and initiated calls to review proposed protocol for both clinical projects and recommendations from EABs meeting. There have been five calls completed, October 17, December 13, 2011, February 6, March 28, June 29, 2012, and September 25, 2012.
- Established Protocol Team at BU and ACRIN to develop and modify study protocols

- Recruited and hired four research associates who will be contract employees at the MTFs
- Developed tracking mechanism between biorepositories and ACRIN DMC
- Administering web user names, passwords, and reader IDs to all appropriate site research personnel
- Developed site readiness tracking tool and continuously updating
- Ordered biomarker collection supplies, preparing biospecimen collection packs for the nodule and screening protocols, in the process of distributing to sites.
- Developed study initiation training conference material
- Conducted site training session via web conference
- Established electronic mail distribution lists and postal directories between the coordinating center and subcontractors and the coordinating center and participating sites
- Established protocol team teleconference schedule
- Had first in person meeting with the EAB at Fort Dettrick, MD, on November 2, 2011, to review the proposed study protocols and have amended both protocols based on feedback received from the EAB and DoD.
- Held second EAB meeting via teleconference on April 23, 2012. Discussion based around molecular biomarkers, protocol submission, addition of cross-sectional cohort, questionnaire, and electronic Case Report Forms. We have amended questionnaire and forms based on feedback from EAB
- Established a schedule for teleconference or in-person bi-annual meetings of the EAB and Steering committee
- Executed consortium subcontracts between coordinating center and:
  American College of Radiology, Mitchell Schnall, PI, 1818 Market St, Philadelphia, MA, involves human subject research
  Brown University, Constantine Gatsonis, PI, 121 South Main Street, Providence, RI, involves human subject research
  The University of Texas M.D. Anderson Cancer Center, **Ignacio I. Wistuba, PI, 1515 Holcombe Blvd, Unit 176 Houston, TX 77030-4009, involves human subject research**
  Regents of the University of California LA, Steve Dubinett, PI, The Regents of the University of California, 11000 Kinross Ave, Ste 102 Los Angeles, CA 90095-1406, involves human subject research
  Executed contracts between coordinating center and participating clinical sites:
  Boston VA Research Institute, Inc, R. Goldstein, 150 S. Huntington Avenue Boston, MA 02130, involves human subject research
  Dallas VA Research Corporation, J. Battaile, 4500 South Lancaster Road, Bldg 43, Suite 124, Dallas, TX 75216, involves human subject research
  Denver Research Institute, R. Keith, VAMC-151 1055 Clermont Street Denver, CO 80220, involves human subject research
  Trustees of University of Pennsylvania (Philadelphia VA Medical Center), A. Vachani, Philadelphia VA Medical Center, 3900 Woodland Avenue, Philadelphia, PA 19104, involves human subject research
  Regents of the University of California LA (Los Angeles VA Healthcare System), S. Dubinett, West Los Angeles Medical Center, 11301 Wilshire Blvd, Los Angeles, CA 90073, involves human subject research
  Veterans Research Foundation of Pittsburgh, C. Atwood, 7180 Highland Drive, Pittsburgh, PA 15240, involves human subject research
  Health Research Inc. Roswell Park Division, M. Reid, Roswell Park, 666 Elm Street, Buffalo, NY, 14263
- Executing consortium subcontracts between coordinating center and:

Middle Tennessee Research Institute (Vanderbilt University), Pierre Massion, PI, 1310 24th Ave S., Rm F-201 Nashville, TN 37212, involves human subject research

- Executing contracts between coordinating center and participating clinical sites:
  Middle Tennessee Research Institute, P. Massion, 1310 24th Avenue South, Nashville, TN 37212, involves human subject research
- Coordinating with participating MTFs:
  Naval Medical Center Portsmouth, 620 John Paul Jones Circle, Portsmouth, VA, 23708-2197, involves human subject research
  Naval Medical Center San Diego, Naval Medical Center, 34800 Bob Wilson Drive, San Diego, CA 92134, involves human subject research
  San Antonio Military Medical Center: Brooke Army Hospital, 3851 Roger Brooke Dr., Fort Sam Houston, TX 78234 and Wilford Hall Medical Center, 2200 Bergquist Drive, Suite 1, Lackland AFB, TX 78236-9908, involves human subject research (CRADA executed)
  Walter Reed National Military Medical Center, Walter Reed Army Medical Center, 6900 Georgia Ave NW, Washington, DC 20307, involves human subject research (CRADA Executed)

3d Site Activities

- Distributed first protocol to each site. Each site has submitted protocol to local IRBs. Full approval: LA VA
- Distributed second protocol to each VA site.
- Confirmed central IRB review of second protocol for MTFs.
- Identified staff that will serve as coordinator for DECAMP protocols; submit all information to coordinating center on standardized form to facilitate communication between the coordinating center and participating sites.
- Subawards include the execution of site contracts for fixed infrastructure support and per case reimbursement

3f Biostatistics and Data Management Center

- Finalized CRFs.

3g Imaging Core Lab

- Finalized CRFs associated with image submission

3i Biospecimen Labs

- Established SOPs and workflow for the biospecimen repository at BU
- Developed tracking system for all samples

Task 4 Clinical Trial Accrual

4a Coordinating Center-General

- Site webinar training completed October 2012
- Monitoring sites as all readiness requirements are satisfied

4b Coordinating Center-Data Management Center

- Baseline forms, program, and follow-up forms activated

4c Coordinating Center-Imaging Core Laboratory

- Confirmed site needs for image transfer, including software and equipment

- Defined imaging parameters
- Developed formal imaging management plan

4e Coordinating Center-Biospecimen Core labs
- Obtained required equipment for analysis
- Trained core lab staff on SOPs and workflow
- Provided training for site coordinators

Key Research Accomplishments:
n/a

Reportable Outcomes:
-Abstract: Spira, University of Pittsburgh, July 2012 (Appendix)

Conclusion:
During our first year, we have successfully developed the infrastructure needed to launch both clinical trials including establishment of detailed protocols, SOPs and CRFs for both studies. We have further developed the administrative workflow to support clinical and imaging data collection at each site along with biosample collection and shipping. Protocol 1 has been approved by HRPO, ACRIN and a number of clinical sites, and sites are positioned to begin enrollment of patients within the next month. Protocol 2 has been approved by HRPO and ACRIN and has been submitted to the local IRBs. We have also established a steering committee, external advisory board, and protocol team to facilitate communication within the consortium and guide efforts to further develop biomarkers for the early detection of lung cancer in both studies.

The Detection of Early Lung Cancer Among Military Personnel (DECAMP) consortium

Spira A[1], Maple E[1], Schnall M[3], Mahon I[3], Apgar C[3], Browning R[15], More K[16], Morris M[17], Parrish JS[18], Atwood C[12], Battaile J[6], , Garshick E[4], Gatsonis C[5], Goldstein R[4], Keith R[7], Lenburg M[1], , Reid M[13], Remick D[2], Vachani A[11], Wistuba I[8] , John Minna[19] , Massion P[10] , Dubinett S[14] on behalf of the DECAMP Consortium

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The Detection of Early lung Cancer Among Military Personnel (DECAMP) consortium is a DOD-funded translational research program to develop and validate molecular biomarkers that can serve as tools for the early detection of lung cancer. While the recent NLST study demonstrated that screening for lung cancer by low-dose CT leads to a significant reduction of lung cancer specific mortality, biomarkers are needed to 1) determine which of the frequently detected lung nodules on CT scan are malignant and 2) how to further define the large high-risk population that would be eligible for screening by CT to increase the efficacy of screening and to reduce the cost and morbidity associated with it. The DECAMP consortium seeks to address these two major gaps in the early detection of lung cancer. First, the consortium will validate a number of airway and blood-based molecular biomarkers that can distinguish benign vs. malignant diseases among smokers with indeterminate pulmonary nodules found on CT chest (i.e. the diagnostic setting). We will recruit 500 smokers with indeterminate pulmonary nodules (0.7cm-2cm) on chest CT who will undergo fiberoptic bronchoscopy on enrollment and will be followed for 2 years until a final diagnosis is made. Our second study will develop and test relatively non-invasive molecular markers in the airway and blood that can identify those smokers at highest risk for developing cancer (i.e. the screening setting). We will recruit 1000 high-risk smokers who will be followed for approximately 4-years for development of lung cancer, all of whom will undergo low-dose CT scan of the chest and non-invasive biospecimen collection annually for the first three years as well as have bronchoscopy performed upon enrollment and at 2 years of follow-up. In addition, the DECAMP consortium will establish a unique high quality biological (including bronchial airway brushings and biopsies, nasal and buccal brushings, blood, urine and sputum), clinical and imaging repository from patients at military and Veterans hospitals across the US (including 4 Military Treatment facilities and 7 Veterans Administration Hospitals) all acquired following the exact same SOPs and securely deposited to support these 2 studies and future correlative studies.